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Copper-catalyzed enantioselective interrupted azide–alkyne cycloaddition to access axially chiral diaryl ethers

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While transition metal-catalyzed enantioselective azide–alkyne cycloadditions are well-established for accessing 1,4-disubstituted triazoles, the direct enantioselective synthesis of chiral 1,4,5-trisubstituted triazoles from terminal alkynes *via* an interrupted process remains largely underdeveloped. Herein, we report a copper-catalyzed enantioselective interrupted azide–alkyne cycloaddition. This method enables the facile construction of enantioenriched axially chiral diaryl ethers bearing a 1,4,5-trisubstituted triazole moiety directly from terminal alkynes. Mechanistic studies reveal the absence of a further kinetic resolution process involving the product, underscoring the crucial role of our newly developed chiral ligand **L5** in achieving excellent enantiocontrol and yield. The combination of Et_3N and LiO^tBu is essential for the inhibition of protonated byproducts. The orthogonal reactivity of the residual terminal alkyne and amine groups within the products provides versatile platforms for downstream chemistry, enriching the structural diversity of axially chiral diaryl ethers.

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Introduction

Over the past few decades, transition metal-catalyzed cycloaddition reactions between alkynes and azides have advanced significantly for the synthesis of functionalized triazoles, following the pioneering independent reports by the Meldal and Sharpless groups.[1] Among these, copper-catalyzed azide–alkyne cycloadditions (Cu-AAC) have been extensively employed to construct diverse chiral molecules bearing 1,4-disubstituted triazole moieties, including those featuring central, axial, planar, and inherent chirality (Scheme 1a).[2] Nevertheless, mechanistic constraints inherently limit this reaction to produce only the 1,4-disubstituted triazoles. Recently, significant progress has been made by the Zhou, Topczewski, Xu, Li, and Cui groups[3] towards the asymmetric synthesis of 1,4,5-trisubstituted triazoles containing central and axial chirality (Scheme 1b), utilizing transition-metal catalyzed azide–alkyne cycloadditions (TM-AAC). However, these approaches typically require the use of electronically activated internal alkynes, hampering their application to some extent. In contrast, a copper-catalyzed interrupted click reaction offers a versatile strategy for constructing 1,4,5-trisubstituted triazoles directly from terminal alkynes (Scheme 1c).[4] In this process, interception of the cuprate–triazole intermediate (**INT-A**) by an electrophile enables the introduction of a substituent at the C5-position. Despite this versatility, current interrupted click methodologies mainly yield achiral products. Very recently, Gu and coworkers developed the first asymmetric interrupted CuAAC reaction with terminal alkynes, cyclic diaryliodonium reagents and azides, providing an efficient method to construct atropisomeric biaryl triazoles.[4k] Given the central role of trisubstituted triazoles as structural scaffolds in bioactive molecules, catalysts, and ligands (Scheme 1d),[5] further development of the enantioselective interrupted click reaction constitutes a critical research priority.

Diaryl ether skeletons constitute important structural motifs prevalent in diverse natural products, ligands, and bioactive molecules.[6] Compared to the well-established synthesis of C–C axially chiral compounds, the development of methods for constructing C–O axial chirality remains challenging.[7] This lag stems from inherently lower rotational barriers and the unique dual-axial chirality phenomenon. Recent years have witnessed rapid progress in the atroposelective synthesis of axially chiral diaryl ethers,[8] primarily achieved through organocatalyzed[9] and transition-metal-catalyzed[10] enantioselective desymmetric functionalization of prochiral substrates. Leveraging sequential enantioselective desymmetrization and kinetic resolution processes has enabled the construction of target axially chiral diaryl ethers with excellent enantioselectivities. However, the inevitable formation of double-functionalization byproducts from the prochiral substrates often compromises reaction yield.[11] Inspired by these elegant studies, we envisioned that the **INT-B** might be captured by an electrophile, for example

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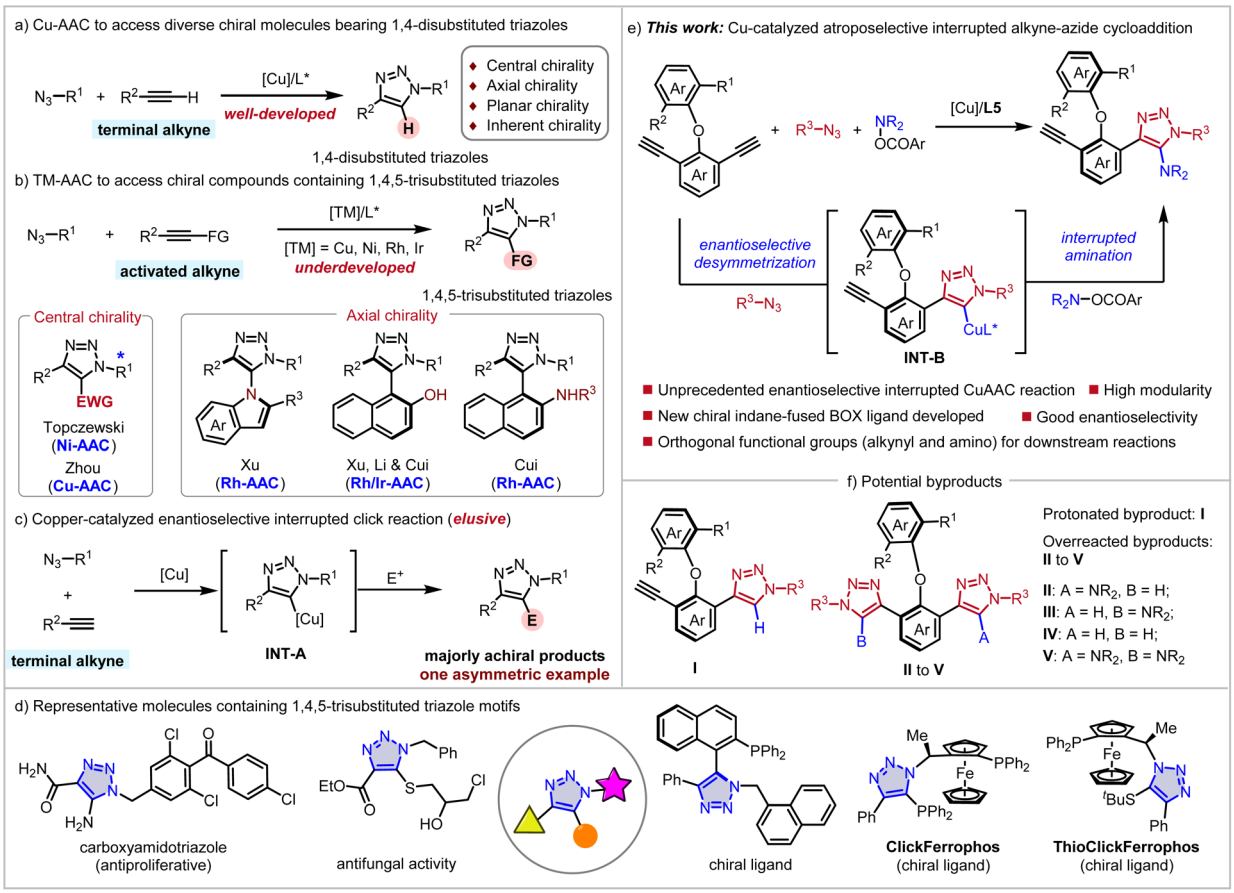


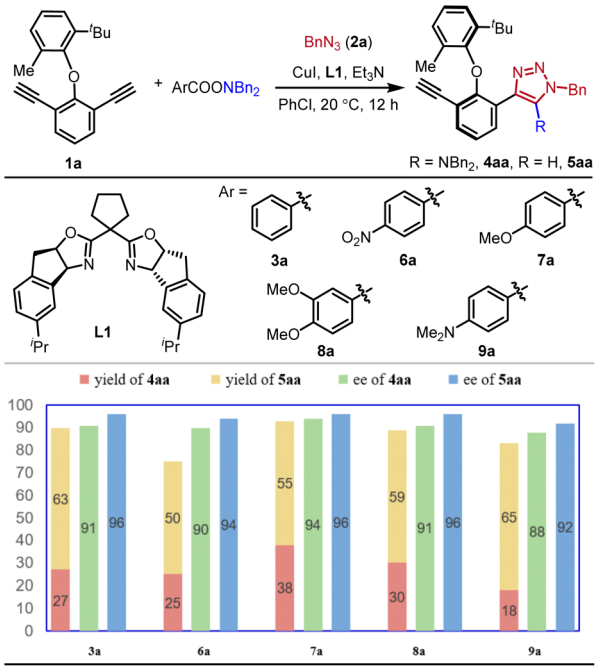
Scheme 1 Transition-metal catalyzed enantioselective (interrupted) azide–alkyne reactions to access axial chirality. (a) Cu-AAC to access diverse chiral molecules bearing 1,4-disubstituted triazoles. (b) TM-AAC to access chiral compounds containing 1,4,5-trisubstituted triazoles. (c) Copper-catalyzed enantioselective interrupted click reaction. (d) Representative molecules containing 1,4,5-trisubstituted triazole motifs. (e) This work: Cu-catalyzed atroposelective interrupted alkyne-azide cycloaddition. (f) Potential byproducts.

a hydroxylamine ester (Scheme 1e).[12] However, to realize this reaction, several challenges must be addressed: (1) how to suppress the formation of byproduct **I** *via* protonation of intermediate **INT-B** (Scheme 1f); (2) the alkyne motif of the product could engage in further reactions with azides and hydroxylamine esters to generate overreacted byproducts **II–V**. Based on our continuous interest in the transition-metal catalyzed enantioselective desymmetrization and synthesis of axial chirality,[13] we report herein an unprecedented copper-catalyzed enantioselective interrupted click reaction. Both protonated and overreacted byproducts **I–V** were inhibited efficiently *via* the development of an indane-fused BOX ligand. The axially chiral diaryl ethers containing 1,4,5-trisubstituted triazole motifs were constructed in good yields with excellent enantiopurities. The orthogonal chemical activities of alkynyl and amino motifs provided platforms for further elaboration of products, enabling the enrichment of the structural diversity of products.

Results and discussion

We commenced our studies using alkyne **1a**, azide **2a** and hydroxylamine ester **3a** as the substrates, CuI as the catalyst and Et_3N as the additive. Initial screening of the chiral ligand indicated that the indane-fused BOX ligand **L1** showed the best performance in the control of enantioselectivity (see the SI for details). The target product **4aa** was obtained in 27% yield with 91% ee, accompanied by the formation of protonation byproduct **5aa** in 63% yield with 96% ee (Scheme 2). To explore the potential influence of the hydroxylamine ester's acyl group on the yield and enantioselectivity of **4aa**, various esters (**6a–9a**) were evaluated. While **6a**, bearing a *para*-electron-withdrawing group, afforded **4aa** in 25% yield with 90% ee, **7a** (containing a *para*-electron-donating group) increased the yield to 38% with a marginal improvement in enantioselectivity. However, further increasing the electron density of the acyl group (**8a** and **9a**) did not enhance the results. The consistently low yield of **4aa** is primarily attributed to the predominant formation of the protonated byproduct **5aa**. The higher enantiopurity observed for **5aa** compared to **4aa** suggested the possible involvement of an inefficient kinetic resolution process in the formation of **4aa**, and subsequent mechanistic studies confirmed that no kinetic resolution occurred.

To suppress the formation of the protonated byproduct **5aa**, other reaction parameters were further evaluated. Solvents

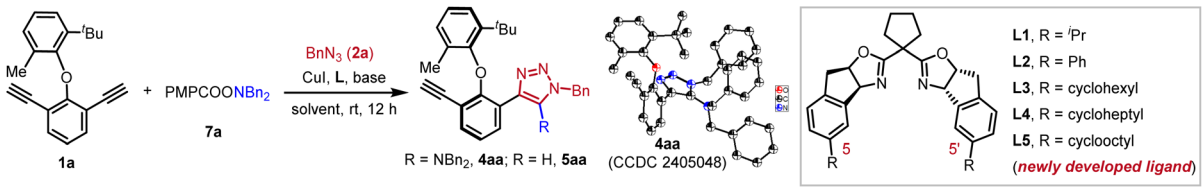


Scheme 2 Initial attempt.

including THF, toluene, and anisole predominantly yielded **5aa** (Table 1, entries 1–3). In contrast, acetone delivered **4aa** and **5aa** with comparable yields (entry 4). Increasing the loading of Et_3N to 10 equivalents marginally improved the yield of **4aa** (entry 5). Further base screening revealed that DIPEA or LiO^tBu suppressed **5aa** formation but significantly reduced either the yield or enantioselectivity of **4aa** (entries 6 and 7). Crucially, employing a combination of Et_3N (10 equiv) and LiO^tBu (0.5 equiv) afforded **4aa** in 87% yield with 88% ee, while only trace amounts of **5aa** were generated (entry 8). Goldup and co-workers reported that the protonation rate of the Cu(I) triazolide intermediate **INT-A** shown in Scheme 1c was highly dependent on the acidity of the proton source.[14] On this basis, we reasoned that combining ^{t}BuOLi with Et_3N could prevent the formation of acidic proton shuttles such as $[Et_3NH]^+$ species, thereby suppressing the protonation of **INT-A** and minimizing the formation of byproduct **5aa**. Encouraged by this result, additional chiral indane-fused BOX ligands bearing various substituents at the C5- and C5′-positions were evaluated (entries 9–12). Generally, enantioselectivity increased with greater steric bulk of the chiral ligand. Among these, **L5** bearing cyclooctyl groups delivered optimal performance, providing **4aa** in 83% isolated yield with 93% ee, and no protonated byproduct **5aa** was detected. The absolute configuration of **4aa** was unambiguously determined by X-ray crystal analysis.

With the optimized conditions in hand, we next explored the substrate scope of prochiral diaryl ether backbones and azides, and the results are summarized in Tables 2A and B. Diaryl ether backbones containing a substituent at the C4- or C4′-position such as halogen, alkyl and aryl groups proceeded smoothly, giving **4ba–4ja** in 74–90% yields with 91–94% ee. Switching the methyl group of **1a** to ethyl and cyclopropyl groups has no effect on the reaction efficiency, delivering **4ka** in 86% yield with 92% ee and **4la** in 85% yield with 96% ee. When the *tert*-butyl group was switched to a 1-adamantanyl group, **4ma** was isolated in 77% yield with moderate enantioselectivity. Upon introducing

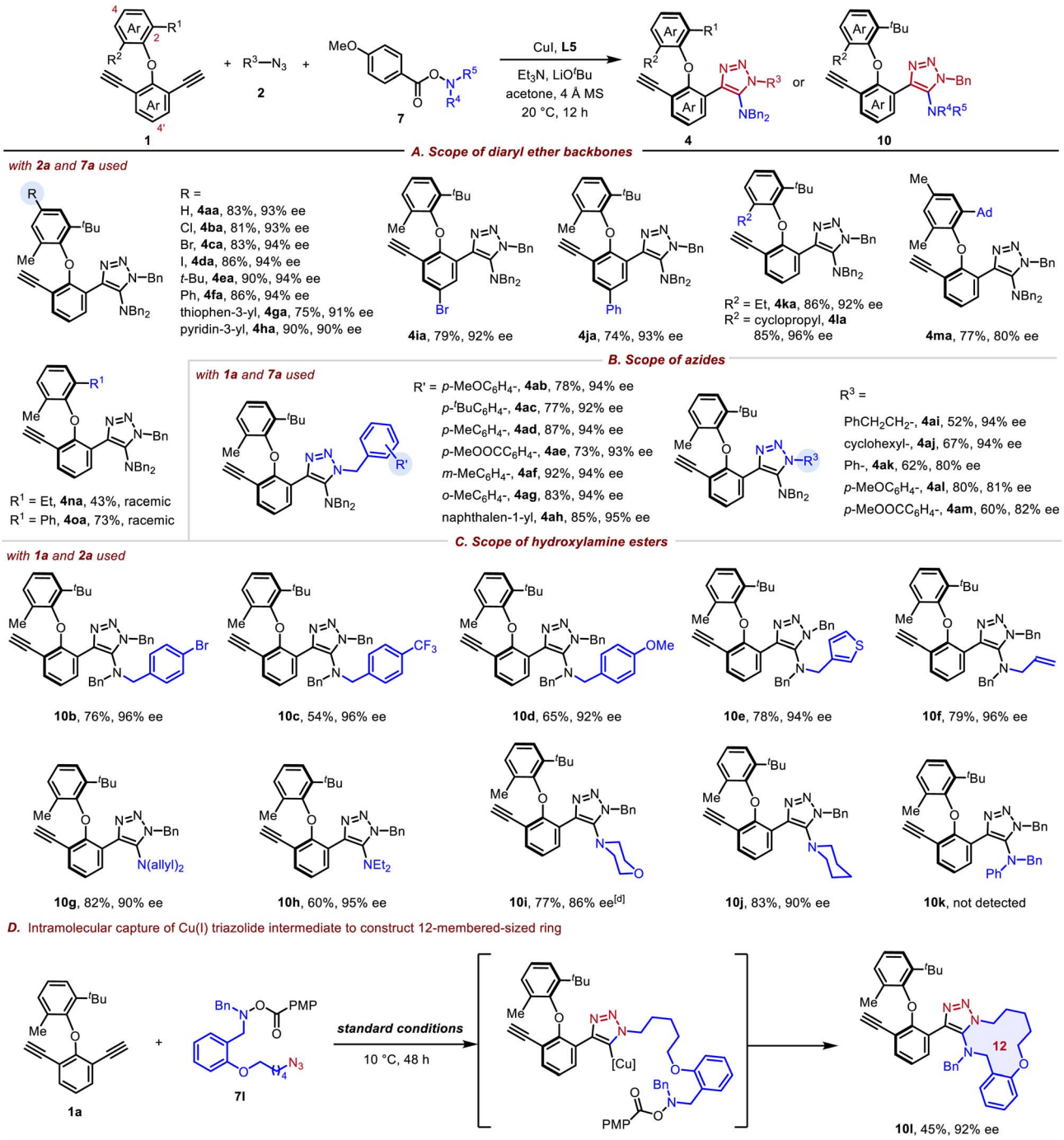
Table 1 Optimization of reaction conditions[a,b,c]



Entry	Ligand	Solvent	Base	Yield (%) (**4aa**/**5aa**)	ee (%) (**4aa**)
1	**L1**	THF	Et_3N	15/10	86
2	**L1**	PhMe	Et_3N	22/39	91
3	**L1**	PhOMe	Et_3N	14/83	87
4	**L1**	Acetone	Et_3N	42/38	87
5[d]	**L1**	Acetone	Et_3N	46/50	86
6	**L1**	Acetone	DIPEA	8/—	86
7	**L1**	Acetone	LiO^tBu	47/—	23
8[d,e]	**L1**	Acetone	Et_3N/LiO^tBu	87/—	88
9[d,e]	**L2**	Acetone	Et_3N/LiO^tBu	48/—	87
10[d,e]	**L3**	Acetone	Et_3N/LiO^tBu	87/—	92
11[d,e]	**L4**	Acetone	Et_3N/LiO^tBu	80/—	93
12[d,e]	**L5**	Acetone	Et_3N/LiO^tBu	91(83)[f]/—	93

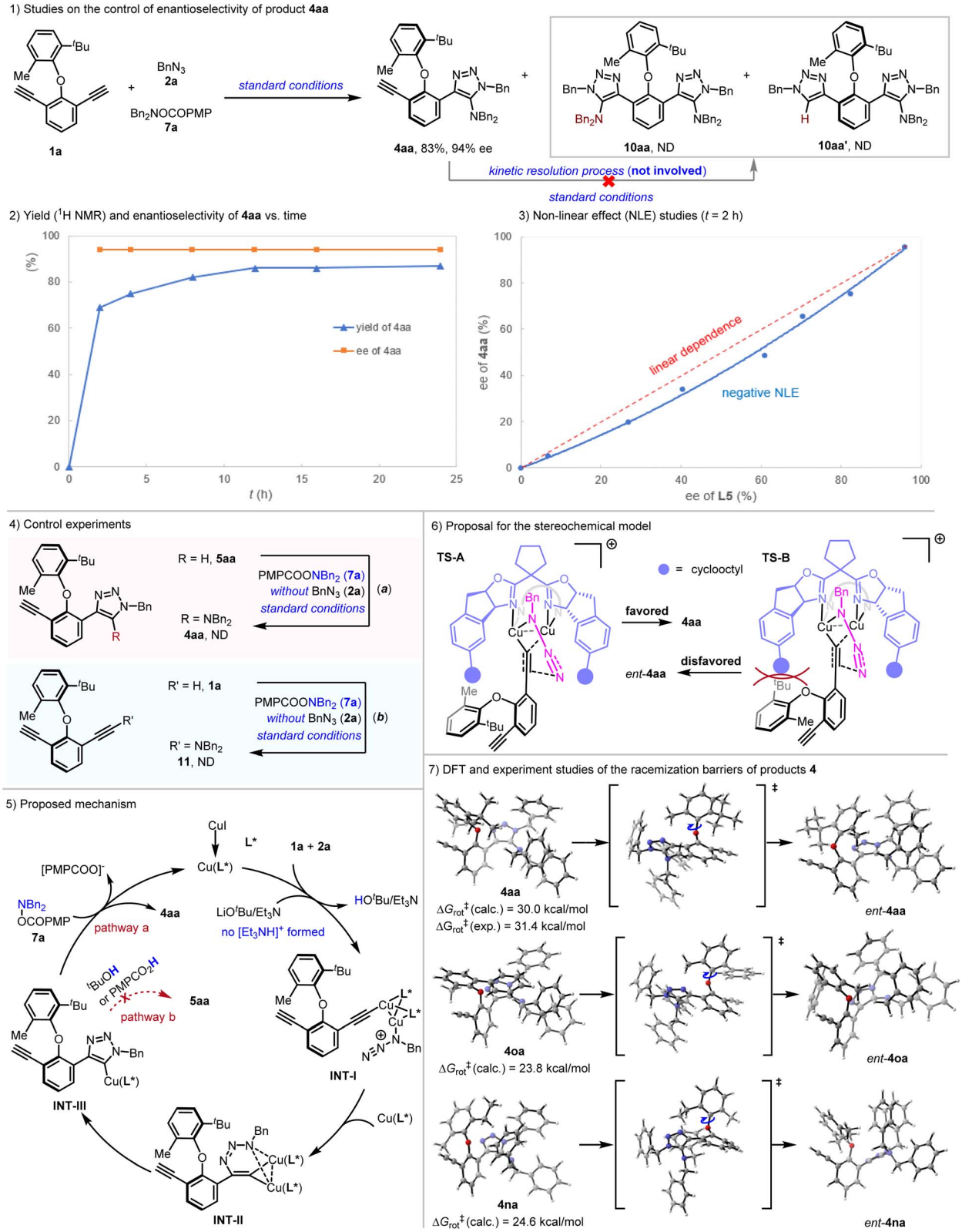
[a] Reaction conditions: **1a** (0.2 mmol and 1.0 equiv), **2a** (0.3 mmol and 1.5 equiv), **7a** (0.4 mmol and 2.0 equiv) CuI (10 mol%), **L** (15 mol%), 4 Å MS (100.0 mg) and base (0.4 mmol and 2.0 equiv) in solvent (1.0 mL) at 20 °C under an Ar atmosphere for 12 h. [b] The yields were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard. [c] ee values were determined by chiral HPLC analysis on a chiral-stationary-phase. [d] Et_3N (2.0 mmol and 10.0 equiv) was used. [e] LiO^tBu (0.1 mmol and 0.5 equiv) was used. [f] Isolated yield was listed.

Table 2 Substrate scope of bisalkynes, azides and hydroxylamine esters[a,b,c]



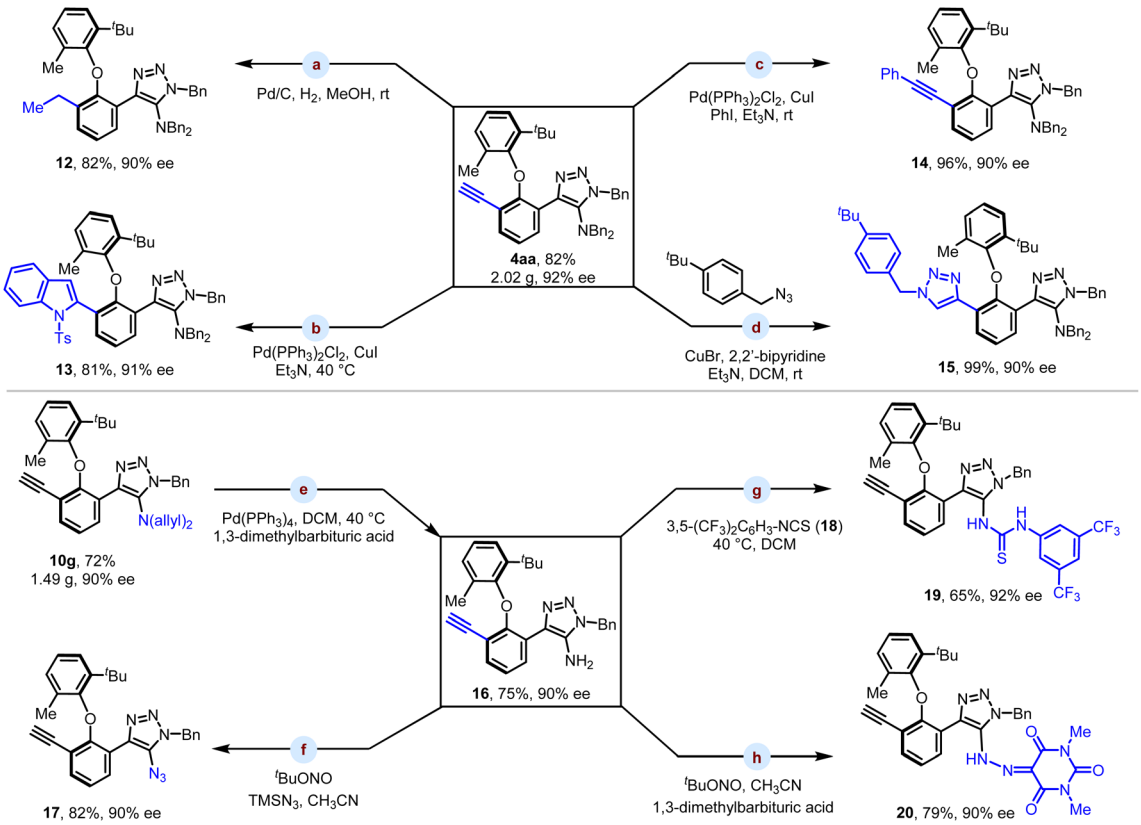
[a] Reaction conditions: **1** (0.2 mmol and 1.0 equiv), **2** (0.3 mmol and 1.5 equiv), **7** (0.4 mmol and 2.0 equiv), Et_3N (2.0 mmol and 10.0 equiv), LiO^tBu (0.1 mmol and 0.5 equiv), CuI (10 mol%), **L5** (15 mol%) and 4 Å MS (100.0 mg) in acetone at 20 °C under an Ar atmosphere for 10 h. [b] Isolated yields were listed. [c] ee values were determined by chiral HPLC analysis on a chiral-stationary-phase. [d] **L1** (15 mol%) was used.

an ethyl or phenyl group at the C2-position, 'Batman'-type chromatograms[15] were observed for products **4na** and **4oa** during HPLC analysis (see the SI for details), indicating interconversion of enantiomers on the chromatographic timescale. Furthermore, benzyl azides containing an electron-donating group or electron-withdrawing group at the *para*-, *meta*- and *ortho*-positions of the phenyl ring as well as 1-(azidomethyl) naphthalene were suitable substrates, furnishing **4ab–4ah** in 73–92% yields with 92–95% ee. In addition, alkyl azides were well compatible, affording **4ai** in 52% yield and **4aj** in 67% yield



Scheme 3 Further studies.

with 94% ee. With aryl azides used, the enantioselecitvities decreased slightly, and products **4ak–4am** were obtained in 60–80% yields with 80–82% ee. The substrate scope of hydroxylamine esters was further investigated (Table 2C). Hydroxylamine esters containing various substituted benzyl, chain alkyl, allyl as well as cyclic alkyl groups were well



Scheme 4 Gram scale synthesis and chemoselective transformations of the products.

compatible with our catalytic system, furnishing the products **10b–10j** in 54–82% yields with 86–96% ee. However, aromatic hydroxylamine esters are incompatible with the current reaction system, and no product (**10k**) was detected. By tethering the azide and hydroxylamine ester motifs within a single molecule, this interrupted click reaction could still proceed smoothly, affording the corresponding 12-membered ring product **10l** in 45% yield with 92% ee (Table 2D). However, further attempts to synthesize the six-membered ring failed under this catalytic system.

Control experiments were then conducted to elucidate the enantioselectivity control and mechanism of this copper-catalyzed enantioselective interrupted reaction. As shown in Scheme 3(1), no over-reacted byproducts **10aa** and **10aa′** were observed under standard conditions. When product **4aa** was subjected to the reaction system, neither **10aa** nor **10aa′** was detected. Plotting of the yield and enantioselectivity of product **4aa** against the reaction time revealed that the reaction rate decreased significantly after 2 hours. The enantioselectivity of compound **4aa** was maintained at 94% and did not improve even after extending the reaction time to 24 hours (Scheme 3(2)). Collectively, these results indicate the absence of further kinetic resolution of **4aa**. Thus, enantioselectivity is exclusively controlled by the desymmetrization process. Reactions carried out using different enantiopurities of ligand **L5** for 2 hours show a negative non-linear effect (NLE),[16] hinting that heterochiral dimeric species is more reactive than the corresponding homodimer (Scheme 3(3)). Moreover, no **4aa** could be detected without addition of BnN_3 (**2a**) under standard conditions, indicating that **5aa** was not the intermediate of this interrupted reaction (Scheme 3(4-a)). In addition, dialkyne **1a** did not participate in the reaction with **7a** in the absence of **2a**, and no ynamine **11** was generated (Scheme 3(4-b)). Therefore, the possibility of a ynamine as an intermediate for this reaction could be ruled out, and the amino motif of the product **4aa** should be introduced *via* the Cu(I) triazolide intermediate (**INT-III** shown in Scheme 3(5)). Based on previous reports[1,17] and our control experiments, a plausible mechanism was proposed and depicted in Scheme 3(5). In the presence of LiO^{t}Bu and Et_3N, the terminal alkyne groups of **1a** react with Cu(L*) to form acetylide intermediate **INT-I**. Intramolecular migratory insertion of **INT-I** first forms the six-membered copper metallacycle **INT-II**, which then undergoes ring contraction to afford the Cu(I) triazolide intermediate **INT-III**. At this stage, two competitive pathways may occur. In pathway a, trapping of **INT-III** with hydroxylamine ester **7a** directly yields the aminated product **4aa**. When a bulky chiral ligand such as **L5** is employed, no over-reacted byproducts are formed. Alternatively, pathway b involving protonation could take place in the presence of a proton source. Given that ^{t}BuOH and $PMPCO_2H$ are the major proton sources present, the protonation of **INT-III** is expected to be sufficiently slow to shut down pathway b. In addition, the origin of the enantioselectivity observed in this interrupted azide–alkyne cycloaddition in the presence of **L5** was

rationalized by considering two competing transition-states, **TS-A** and **TS-B**. For **TS-B**, severe repulsion arises between the cyclooctyl group of chiral ligand **L5** and the *tert*-butyl group of substrate **1a** (Scheme 3(6)).

Subsequently, the configurational stability of **4** was studied *via* DFT calculations (Scheme 3(7)). As expected, the rotational barrier of the C(1)–O bond generally increased with greater steric hindrance from the *ortho*-substituent. Computational studies provided rotational barriers of 23.8 kcal mol^{-1} for **4oa**, 24.6 kcal mol^{-1} for **4na**, and a significantly higher barrier of 30.0 kcal mol^{-1} for **4aa**. The relatively low barriers for **4oa** and **4na** rationalize their facile racemization. This interpretation is corroborated by thermal racemization studies of enantiopure **4aa**, which exhibited a half-life of 32.1 hours at 100 °C in toluene. The experimentally determined rotational barrier of **4aa** *via* a thermal experiment was 31.4 kcal mol^{-1}, which was in agreement with the computed value of 30.0 kcal mol^{-1}.

The practical utility of our reaction was further explored *via* scale-up reactions and derivatization studies of the alkyne and amino motifs of the products (Scheme 4). When the reactions were run on a 4 mmol-scale, the catalyst loading could be further reduced to 2.5 mol% without any loss of efficiency. The products **4aa** and **10g** were isolated in 82% yield (2.02 g) and 72% yield (1.49 g), respectively, with comparable enantioselectivity. The alkyne group was chemoselectively reduced to an ethyl group with Pd/C under hydrogen balloon conditions without affecting the benzyl group, yielding product **12** in 82% yield and 90% ee (Scheme 4a). In addition, transition-metal catalyzed cross-coupling such as Larock indole synthesis, Sonogashira coupling and alkyne–azide cycloaddition proceeded smoothly, delivering compounds **13–15** in 81–99% yields with 90–91% ee (Scheme 4b–d). Palladium-catalyzed deallylation of **10g** proceeded smoothly, giving free amine **16** in 75% yield with 90% ee (Scheme 4e). The amino group could further undergo azidation in the presence of ^{t}BuONO and $TMSN_3$, delivering product **17** in 82% yield with 90% ee (Scheme 4f). Treatment of **16** with isothiocyanate **18** afforded thiourea **19**, which was isolated in 65% yield with 92% ee (Scheme 4g). In addition, the primary amino motif of **16** could react with barbituric acid and ^{t}BuONO in an acetonitrile solvent to generate hydrazone **20** in 79% yield with 90% ee (Scheme 4h).

Conclusions

In summary, we have developed a copper-catalyzed enantioselective desymmetric interrupted alkyne–azide cycloaddition with dialkynes, azides and hydroxylamine esters. This method provides direct access to a series of axially chiral diaryl ethers bearing 1,4,5-trisubstituted triazole motifs in good yields with high modularity. Employing a newly designed indane-fused BOX ligand **L5**, C–O axially chiral scaffolds are constructed with excellent enantioselectivity. Notably, the over-reacted reactions are effectively blocked using a LiO^{t}Bu and Et_3N dual-base system. Control experiments demonstrate the absence of kinetic resolution processes in enhancing product enantiopurity. The orthogonal reactivity of the residual alkyne and amino groups in products offers a versatile synthetic handle for downstream diversification.

Author contributions

R. W., L. C., Y. C., Q. W., and Q. C. performed all chemical reactions reported, Q. L. contributed to the DFT calculations and A. L., H. Y., Q. L. and S. G. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI), including detailed experimental procedures and characterization data for new compounds and computational methods. Supplementary information is available. See DOI: https://doi.org/10.1039/d5sc09566b.

CCDC 2405048 (**4aa**) contains the supplementary crystallographic data for this paper.[18]

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